REMARKS

By the present amendment, claims 22, 25, 28, 34, 35, 42, 43, and 49-50 have been amended for purposes of clarity, claims 38, 45, and 51-53 have been canceled without prejudice, and new claims 57-68 have been added.

Applicants note that the status of claim 34 was not identified in the Office Action.

Claim 22 has been amended to recite that the reactive group is coupled, optionally via a linking group, to said kringle 5 peptide. Claim 22 has also been amended to recite succinimidyl group in place of succinimidyl-containing group, and to recite maleimido group in place of maleimido-containing group to secure consistency with the recitations in the specification, and without any change to claim scope. Furthermore, claim 22 has been amended to insert "modified" prior to the second occurrence of "kringle 5 peptide" for proper antecedent basis.

Claim 25 has been amended to recite said modified kringle 5 peptide for proper antecedent basis.

Claim 28 has been amended to recite that the maleimido group is coupled, optionally via a linking group, to said kringle 5 peptide.

Claim 34 has been amended to recite a method of preparing a conjugate comprising conjugating a modified kringle 5 peptide *ex vivo* to a blood component, wherein said modified kringle 5 peptide comprises a kringle 5 peptide and a maleimido group coupled, optionally via a linking group, to said kringle 5 peptide, wherein said maleimido group reacts with a thiol group of said blood component to form a covalent bond, and wherein said kringle 5 peptide comprises SEQ ID NO: 8.

Claim 35 has been amended to recite, *inter alia*, that the conjugate is formed by conjugating a modified kringle 5 peptide to a blood component, wherein said modified kringle 5 peptide comprises a kringle 5 peptide and a maleimido group coupled, optionally via a linking group, to said kringle 5 peptide, wherein said maleimido group reacts with a thiol group of said blood component to form a covalent bond. Claim 35 has been amended to recite a maleimido group because such a reactive group forms a stable thioether linkage when reacted with a thiol group on a blood component (*see, e.g.*, p. 12, lines 1-5). Furthermore, claim 35 recites that the kringle 5 peptide comprises SEQ ID NO: 8.

Claim 42 has been amended to delete the recitation that the composition is for providing an anti-angiogenic effect to a patient because the recitation does not further limit the claim. Claim 42 has also been amended to recite the conjugate of claim 35 instead of a

conjugate of claim 35 for proper antecedent basis.

Claim 43 has been amended so that it now recites a composition comprising the conjugate of claim 36 in association with a pharmaceutically acceptable carrier.

Claim 49 has been amended to has been amended to recite, *inter alia*, that the conjugate is formed by conjugating a modified kringle 5 peptide to albumin, wherein said modified kringle 5 peptide comprises a kringle 5 peptide and a maleimido group coupled, optionally via a linking group, to said kringle 5 peptide, wherein said maleimido group reacts with a thiol group of said albumin to form a covalent bond. Furthermore, claim 49 recites that the kringle 5 peptide comprises SEQ ID NO: 8.

Claim 50 has been amended to recite succinimidyl group in place of succinimidyl containing group to secure consistency with the recitations in the specification.

Claim 38 has been canceled as being redundant with claim 36. Claim 45 has been canceled as being redundant with claim 42. Claim 51 has been amended as being redundant with claim 28. Claim 53 has been canceled as being redundant with claim 35.

New claims 57-68 have been added to claim particular embodiments of the invention.

The amendments to the claims and the new claims are supported in the specification as set forth in the table below.

Claim Number **Recitation**	**Support**
22 Optionally via a linking group	p. 6, lines 13-15
Succinimidyl group	p. 4, lines 6-16; p. 11, lines 13-14
Maleimido group	p. 4, lines 6-16; p. 11, lines 24-25
28 Optionally via a linking group	p. 6, lines 13-15
34 Optionally via a linking group	p. 6, lines 13-15
Blood component	p. 7, lines 1-5
Method of preparing a conjugate *ex vivo*	p. 15, lines 1-7
35 Optionally via a linking group	p. 6, lines 13-15
Maleimido group	p. 4, lines 6-16; p. 11, lines 24-25

43	p. 34, lines 10-20
49 Optionally via a linking group	p. 6, lines 13-15
50 Succinimidyl group	p. 4, line 16; p. 11, lines 13-14
57	p. 34, lines 10-20
58	p. 7, lines 1-5; p. 17, lines 4-8; p. 28, lines 14-21
59	p. 7, lines 1-5; p. 17, lines 4-8; p. 28, lines 14-21
60	p. 7, lines 1-5; p. 17, lines 4-8; p. 28, lines 14-21
61	p. 28, line 24
62	p. 28, lines 24-29
63	p. 28, lines 24-32
64	p. 28, line 24
65	p. 28, lines 24-29
66	p. 28, lines 24-32
67	p. 12, lines 6-13
68	p. 12, line 24 – p. 14, line 24

No new matter has been added.

IV. THE REJECTION UNDER 35 U.S.C. § 103(a) OF CLAIMS 35-36, 38, 42-43, 45, 49-53, AND 56 AS BEING UNPATENTABLE OVER DAVIDSON *et al.* IN VIEW OF PEETERS *et al.* SHOULD BE WITHDRAWN

Claims 35-36, 38, 42-43, 45, 49-53, and 56 are rejected as unpatentable under 35 U.S.C. § 103(a) as allegedly being obvious over WO 97/41824 (Davidson *et al.*) in view of Peeters *et al.*, *J. Immunol. Methods* 1989: 120, 133-143 (Peeters *et al.*). Specifically, the Examiner states that Davidson *et al.* discloses a kringle 5 peptide having an amino acid

sequence that is 100% identical to the currently claimed peptide comprising SEQ ID NO: 8, and that Davidson *et al.* also teaches a method of producing polyclonal antisera using the kringle 5 peptide linked to BSA using glutaraldehyde in combination with an adjuvant mixture. The Examiner acknowledges that Davidson *et al.* fails to disclose a reactive group which is a maleimido group or a succinimidyl group, but notes that Peeters *et al.* teaches the linker, succinimidyl 6-(N-maleimido)-n-hexanoate (MHS), which is said to have no linker specific antibody reactivity. The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate the kringle 5 peptide to a carrier protein, such as BSA, using MHS as taught by Peeters *et al.* instead of glutaraldehyde to achieve a peptide linked to a carrier protein which generates antibodies which are not directed against the linker. For the following reasons, Applicants respectfully disagree.

In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 U.S.P.Q.2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 U.S.P.Q. at 467; *see also* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* ("Examination Guidelines"), Federal Register, Vol. 72, No. 195, October 10, 2007, pages 57527-57528. The Supreme Court stated that in determining obviousness, "a court must ask whether the improvement is more than a predictable use of prior art elements according to their established functions." *KSR*, 127 S.Ct. at 1740, USPQ2d at 1396. The Supreme Court also stated that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does...." *KSR*, 127 S.Ct. at 1741, 82 U.S.P.Q.2d at 1396.

In the present case, independent claims 35 and 49, recite, *inter alia*, a conjugate formed by conjugating a modified kringle 5 peptide to a blood component (claim 35) or albumin (claim 49), wherein said modified kringle 5 peptide comprises a kringle 5 peptide and a maleimido group coupled, optionally via a linking group, to said kringle 5 peptide. The claims further recite that the maleimido group reacts with a thiol group of said blood

component (albumin in claim 49) to form a covalent bond. Thus, the conjugates recited in these claims are formed by reacting a thiol group of a blood component/albumin with the maleimido group, and thus have chemical structures wherein the modified kringle 5 peptide is attached to the thiol group of the blood component (claim 35) or albumin (claim 49). The recitations in the amended claims that the maleimido group reacts with a thiol group *of* said blood component (claim 35) or *of* said albumin makes it clear that the maleimido group reacts with a thiol group already present as part of the blood component or albumin (*i.e.*, a native thiol group).

The combination of Davidson *et al.* and Peeters *et al.* does not give reason to one of ordinary skill to form a conjugate through covalent binding with a native thiol group of a blood component. Thus, the Examiner's proposed combination would not yield a conjugate having the same chemical structure as the conjugate recited in the claims. As conceded by the Examiner, Davidson *et al.* only teaches conjugates using glutaraldehyde as a crosslinking agent, and thus does not contemplate using thiol groups of the carrier protein. Peeters *et al.* does not remedy this deficiency. Peeters *et al.* teaches peptide-carrier protein conjugates which are used to raise antipeptide antibodies. As explained in detail below, Peeters *et al.* does not teach or suggest reacting native thiol groups (*i.e.*, thiol groups <u>of</u> a blood component) in order to form the peptide-carrier protein conjugates.

Peeters *et al.* discloses three possibilities for modifying a carrier protein in order to make a suitable coupling partner to make conjugates. In the first possibility, Peeters *et al.* teaches that the "amino groups of the protein can be modified to an adjustable extent with an active ester (*e.g.*, a succinimidyl ester) bearing a maleimide moiety" (first full paragraph, col. 1, p. 135 of Peeters *et al.*). The carrier proteins bearing the maleimide groups are then stated to react with peptides bearing a sulphydryl (thiol) group. *Id.* If the peptide does not have a thiol group, it can be added per the disclosure in the last paragraph, col. 1, p. 135. Thus, Peeters *et al.* discloses that the maleimido group reacts with a thiol group of the peptide or added to the peptide, rather than of the carrier protein, whereas claims 35 and 49 recite that the maleimido group reacts with a thiol group of the blood component or albumin. Moreover, in the first possibility disclosed by Peeters *et al.*, amino groups of the carrier protein, and not thiol (sulphydryl) groups of the carrier protein, are used to prepare a suitable coupling partner bearing a maleimide group. Therefore, the resulting conjugate taught by Peeters *et al.* comprises the carrier protein linked at an amino group of the protein, not a thiol

group of the protein, in contrast to the conjugates of claims 35, 49, and their dependent claims.

The second possibility that Peeters *et al.* discloses for modifying a carrier protein to make a suitable coupling partner for making conjugates involves thiolation of the carrier protein by functionalization of a particular amino group (*see* paragraph bridging cols. 1 and 2, p. 135 of Peeters *et al.*), and not by functionalization of a (native) thiol group of the carrier protein. Peeters *et al.* teaches acylating an amino group of a peptide or carrier protein with homocysteine thiolactone, with a succinimidyl ester of S-acetyl thioacetic acid, or with 3-(2-pyridyldithio)propionic acid in order to thiolate the peptide or carrier protein. In explaining that either thiolation or maleylation could be applied to the carrier protein and peptide, Peeters *et al.* notes that the "the peptide and the protein in the latter route are unified through acylation of amino groups." Thus, Peeters *et al.* discloses functionalizing *an amino group of the carrier protein*, and not a thiol (sulphydryl) group of the carrier protein, in order to prepare a suitable coupling partner for preparation of the disclosed conjugates. Such a thiolated carrier protein does not provide a thiol of a blood component for conjugation purposes; rather, it provides a thiol of a chemical appendage derivatizing a blood component for conjugation purposes. Since Peeters *et al.* does not give reason to one of ordinary skill in the art to use a native thiol (sulphydryl) group already present in the carrier protein to form a peptide-carrier conjugate, the disclosure does not suggest the structure of the claimed conjugates, which have a stable thioether linkage formed from reaction of a thiol group of the blood component with the maleimido group on the modified kringle 5 peptide.

Peeters *et al.* discloses a third possibility for forming conjugates which depends on acylation with succinimidyl 3-(2-pyridyldithiopropionate) SPDP (first paragraph, col. 2, p. 135). Since this route depends on forming conjugates using a disulfide link rather than through a maleimido group, Applicants submit it does not teach or suggest the claimed conjugates.

Accordingly, the combination of Davidson *et al.* with Peeters *et al.* does not give reason to prepare the presently claimed conjugates. Moreover, since neither Davidson *et al.* nor Peeters *et al.* disclose a stable thioether linkage formed from reaction of a thiol group of a blood component with a maleimido group on a modified kringle 5 peptide, which characterizes the conjugates recited in the claims, it is clear that the claimed conjugates are not a combination of known elements. *Cf. KSR.*

In view of the foregoing, Applicants respectfully submit that the rejection of claims 35 and 49 and their dependent claims under § 103(a) is in error and respectfully request the Examiner to withdraw the rejection.

CONCLUSION

Entry of the foregoing amendments and remarks into the record of the above-identified application is respectfully requested. Applicants submit that the amendments and remarks made herein now place the application in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

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Respectfully submitted,

Date: April 17, 2008

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Enclosures